REMARKS

Upon entry of the above amendments, claims 1-3 and 10 will be pending in this application. Claims 1, 2 and 10 have been amended. Support for the amendments can be found throughout the application, for example, in originally filed claim 6. Further, the specification at page 15, lines 26-30, defines a "Modified neurotoxin" to mean a neurotoxin comprising a structural modification that changes, e.g. increases, the biological persistence of the modified neurotoxin. Claims 4-7 have been canceled without prejudice. No new matter has been added.

As a preliminary matter, Applicants acknowledge with thanks the withdrawal of the rejection for claims 1-3 and 6 under 35 U.S.C. § 102(b) over WO 96/39166 (Johnson et al.).

I. The claims are fully described by the specification

Claims 1-7 and 10 are rejected under 35 U.S.C. § 112, paragraph 1, as allegedly lacking written description. Specifically, the Office Action alleges at page 3 that, "Applicants have not described a function which is shared by the modified botulinum toxin which would adequately describe the genus."

Applicants respectfully disagree with the allegation of the Office Action. However, for the sole purpose of compact prosecution, the claims have been amended to clarify that the modified botulinum toxin has an "increased biological persistence as compared to the naturally occurring botulinum toxin". Based on the definition provided for the term "biological persistence" in the specification at page 16, one of ordinary skill would understand a modified botulinum toxin that has an "increased biological persistence as compared to the naturally occurring botulinum toxin" to mean a modified botulinum toxin that has an increased time duration in which the modified neurotoxin causes an inhibition of release of neurotransmitters. Moreover, one of ordinary skill would understand that the inhibition of release of neurotransmitter is achieved by the catalytic activity of the botulinum toxin. See the specification, for example, at page 4, lines 4-15. Thus, the amended claims clearly describe a function (i.e., inhibition of

release of neurotransmitters) that is shared by the modified botulinum toxin which would adequately describe the genus.

Further, contrary to the allegation of the Office Action, the degree of modification of the botulinum toxin does have an upper limit. For example, the secondary modification sites can only be added to the botulinum toxin at locations that would not interfere with the toxin's catalytic activity. Moreover, one of ordinary skill would know where to add the secondary modification sites (e.g., phosphorylation sites) to a naturally existing botulinum toxin to increase the biological persistence, without interfering with the catalytic ability of the toxin. For example, one of ordinary skill would add the secondary modification sites to non-critical regions of the toxin. Such non-critical regions are well know prior to the filing date of the present application. These non-critical regions can be determined experimentally by assessing the resulting toxicity of the modified toxin using standard toxicity assays such as that described by Zhou, L., *et al., Biochemistry* (1995) 34:15175-15181, which describes an *in vitro* assay for the ability of light chain to cleave recombinantly produced SNAP-25. Other suitable assays commonly practiced include simple injection into mice to evaluate lethality. These assays are described, for example, by Maisey, E.A., *et al., Eur J. Biochem.* (1988) 177:683-691. Moreover, rational decisions about where to insert the secondary modification sites may be based on the known conformation of the toxins. For example, the crystal structure of botulism toxin type A is described, for example by Lacy, D.B., *et al., Nature Structural Biology* (1998) 5:898-902. Other features of the protein are also known. Recent studies of the BoNT/A light chain have revealed certain features important for the activity and specificity of the toxin towards its target substrate, SNAP-25. For example, studies by Zhou, *et al., Biochemistry* 34:15175-15181 (1995) have indicated that when the light chain amino acid residue His_{227} is substituted with tyrosine, the resulting polypeptide is unable to cleave SNAP-25; Kurazono, *et al., J. Biol. Chem.* 14721-14729 (1992) performed studies in the presynaptic cholinergic neurons of the buccal ganglia of *Aplysia californica* using recombinant BoNT/A light chain that indicated that the removal of 8 N-terminal or 32 C-terminal residues did not abolish

toxicity, but that removal of 10 N-terminal or 57 C-terminal residues abolished toxicity in this system. Most recently, the crystal structure of the entire BoNT/A holotoxin has been solved; the active site is indicated as involving the participation of His_{222}, Glu_{223}, His_{226}, Glu_{261} and Tyr_{365}. Lacy, *et al.*, *supra*. (These residues correspond to His_{223}, Glu_{224}, His_{227}, Glu_{262} and Tyr_{366} of the BoNT/A L chain of Kurazono *et al.*, *supra*.) Interestingly, an alignment of BoNT/A through E and TeNT light chains reveals that every such chain invariably has these residues in positions analogous to BoNT/A. Kurazono, *et al.*, *supra*.

In light of the above described knowledge (which are all published prior to the filing date of the present application), one of ordinary skill in the art would know where to add the secondary modification sites (e.g., phosphorylation sites) to a naturally existing botulinum toxin to increase the biological persistence, without interfering with the catalytic ability of the toxin. Thus, the claims are fully described, and Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 112, paragraph 1.

II. The claims are novel

WO 96/39166 (Johnson et al.):

Claims 4, 5 and 10 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Johnson et al. The cancellation of claims 4 and 5 renders moot the rejection thereof. Applicants respectfully traverse the rejection of claim 10 because Johnson et al. fails to teach or suggest all the features of claim 10. *Glaxo v. Novopharm, Ltd.*, 334 U.S.P.Q.2d 1565 (Fed. Cir. 1995).

Claim 10 is directed to botulinum toxins that have N-glycosylation sites that may be *targeted* by an enzyme, for example an intracellular enzyme, to affect an N-glycosylation to the site. On the other hand, Johnson et al. does not disclose a modified neurotoxin comprising an N-glycosylation sites site that may be the *target of an enzyme* for secondary modification. Instead, Johnson et al. merely reports a botulinum toxin analogue having a more stable acid residue in a pairing at a degradable site. Specifically, Johnson et al. reports that such botulinum toxin analogues have a threonine residue in

place of a tyrosine residue, or an asparagine residue in place of an arginine residue, at the degradable site. Further, Johnson et al. does not disclose or teach that these substitutions will cause an enzyme to target these substituted sites to affect a secondary modification (e.g., phosphorylate) to the botulinum toxin.

Because Johnson et al. fails to teach or suggest every feature of claim 10, claim 10 is not anticipated. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 102(b).

U.S. Patent Number 5,837,265 (Montal et al.)

Claims 1-7 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Montal et al. Applicants respectfully traverse the rejection because Montal et al. fails to teach or suggest all the features of the present invention. *Glaxo v. Novopharm, Ltd.*, 334 U.S.P.Q.2d 1565 (Fed. Cir. 1995).

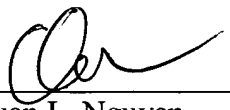
Montal et al. teaches the substitution of the serine, threonine or tyrosine with a glutamate or aspartate. The Office Action cited U.S. Patent Publication No. 2004/0077039 and alleges that such substitution can result in an alle that mimics constitutive phosphorylation. Applicants have reviewed U.S. Patent Publication No. 2004/0077039 and understand that such substitution of a negatively charged amino acid (glutamate or aspartate) may **mimic** the negatively charge phosphorylation. **However, a glutamate or aspartate that mimics a phosphorylated amino acid is not the same as a phosphorylated amino acid.** Applicants cannot find any evidence that such substitution will result in creating a secondary modification site, e.g., a site for phosphorylation.

Thus, Montal et al. does not disclose all the features of the present claims (e.g., secondary modification sites in addition to the ones on unmodified botulinum toxins), Montal et al. cannot anticipate the claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 102(b).

V. Conclusion

In view of the foregoing, Applicants submit that the claims as amended claims are in condition for allowance, and an early Office Action to that effect is earnestly solicited.

Respectfully submitted,



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